

WHAT IS CLAIMED IS:

1. An polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said polypeptide binds an FcγR with an altered affinity relative to a polypeptide comprising a wild-type Fc region, provided that said at least one amino acid modification is not solely a substitution at any of positions 255, 258, 267, 269, 270, 276, 278, 280, 283, 285, 289, 292, 293, 294, 295, 296, 300, 303, 305, 307, 309, 322, 329, 332, 331, 337, 338, 340, 373, 376, 416, 419, 434, 435, 437, 438, 439 or does not have an alanine at any of positions 256, 290, 298, 312, 333, 334, 359, 360, 326, or 430; a lysine at position 330; a threonine at position 339; a methionine at position 320; a serine at position 326; an asparagine at position 326; an aspartic acid at position 326; a glutamic acid at position 326; a glutamine at position 334; a glutamic acid at position 334; a methionine at position 334; a histidine at position 334; a valine at position 334; or a leucine at position 334; a lysine at position 335 an asparagine at position 268; a glutamine at position 272; a glutamine, serine, or aspartic acid at position 286; a serine at position 290; a methionine, glutamine, glutamic acid, or arginine at position 320; a glutamic acid at position 322; a serine, glutamic acid, or aspartic acid at position 326; a lysine at position 330; a glutamine at position 335; or a methionine at position 301.

2. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said polypeptide specifically binds FcγRIIIA with a greater affinity than a comparable polypeptide comprising the wild-type Fc region binds FcγRIIIA, provided that said at least one amino acid modification is not solely a substitution at positions 329, 331, or 332, or does not have an alanine at any of positions 256, 290, 298, 312, 326, 333, 334, 359, 360, or 430; a lysine at position 330; a threonine at position 339; a methionine at position 320; a serine at position 326; an asparagine at position 326; an aspartic acid at position 326; a glutamic acid at position 326; a glutamine at position 334; a glutamic acid at position 334; a methionine at position 334; a histidine at position 334; a valine at position 334; a lysine at position 330; a lysine at position 335; or a leucine at position 334.

3. The polypeptide of claim 2, wherein said at least one amino acid modification comprises a set of substitutions selected from the group consisting of substitution at position 339 with valine and at position 347 with histidine; a substitution at position 251 with proline and at position 415 with isoleucine; a substitution at position 185 with methionine, and at position 218 with asparagine, and at position 292 with leucine, and at position 399

with glutamic acid; a substitution at position 290 with proline and at position 142 with proline; a substitution at position 141 with valine, at position 268 with leucine, at position 288 with glutamic acid, and at position 291 with serine; a substitution at position 133 with methionine, at position 149 with tyrosine, at position 205 with glutamic acid, at position 5 334 with asparagine, and at position 384 with lysine; a substitution at position 125 with leucine, at position 215 with isoleucine, and at position 408 with isoleucine; a substitution at position 395 with isoleucine; a substitution at position of 247 with histidine; a substitution at position 396 with histidine; a substitution at position 392 with arginine; a substitution at position 415 with isoleucine and at position 251 with phenylalanine; a substitution at 10 position 301 with cysteine, at position 252 with leucine, and at position 192 with threonine; a substitution at position 315 with isoleucine; a substitution at position 132 with isoleucine; a substitution at position 162 with valine; a substitution at position 348 with methionine, at position 334 with asparagine, at position 275 with isoleucine, at position 202 with methionine, and at position 147 with threonine; a substitution at position 310 with tyrosine, 15 at position 289 with alanine, and at position 337 with glutamic acid; a substitution at position 119 with phenylalanine, at position 371 with serine, at position 407 with valine, and at position 258 with aspartic acid; a substitution at position 409 with arginine and at position 166 with asparagine; a substitution at position 408 with isoleucine, at position 215 with isoleucine, and at position 125 with isoleucine; a substitution at position 396 with 20 leucine; a substitution at position 385 with glutamic acid and at position 247 with histidine; a substitution at position 379 with methionine; a substitution at position 219 with tyrosine; a substitution at position 282 with methionine; a substitution at position 276 with isoleucine, at position 334 with asparagine, and at position 348 with methionine; a substitution at position 401 with valine; a substitution at position 280 with leucine and at position 395 with 25 serine; a substitution at position 222 with asparagine; a substitution at position 246 with threonine and at position 319 with phenylalanine; a substitution at position 243 with isoleucine and at position 379 with leucine; a substitution at position 246 with threonine and at position 396 with histidine; a substitution at position 268 with aspartic acid and at position 318 with aspartic acid; a substitution at position 288 with asparagine, at position 30 330 with serine, and at position 396 with leucine; a substitution at position 243 with leucine, at position 255 with leucine, and at position 318 with lysine; a substitution at position 334 with glutamic acid, at position 359 with asparagine, and at position 366 with serine; a substitution at position 377 with phenylalanine; a substitution at position 334 with isoleucine; a substitution at position 244 with histidine, at position 358 with methionine, at 35 position 379 with methionine, at position 384 with lysine, and at position 378 with

methionine; a substitution at position 247 with leucine; a substitution at position 217 with serine, at position 378 with valine, and at position 408 with arginine; a substitution at position 247 with leucine, at position 253 with asparagine, and at position 334 with asparagine; a substitution at position 288 with methionine and at position 334 with glutamic acid; a substitution at position 334 with glutamic acid and at position 380 with aspartic acid; a substitution at position 256 with serine, at position 305 with isoleucine, at position 334 with glutamic acid, and at position 390 with serine; a substitution at position 372 with tyrosine; a substitution at position 246 with isoleucine and at position 334 with asparagine; a substitution at position 335 with asparagine, at position 370 with glutamic acid, at position 378 with glutamic acid, at position 394 with methionine, and at position 424 with leucine; a substitution at position 320 with glutamic acid and at position 326 with glutamic acid; a substitution at position 224 with leucine; a substitution at position 375 with cysteine and at position 396 with leucine; a substitution at position 233 with aspartic acid and at position 334 with glutamic acid; and a substitution at position 334 with glutamic acid, at position 359 with asparagine, at position 366 with serine, and at position 386 with arginine.

4. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said polypeptide specifically binds Fc $\gamma$ RIIIA with a greater affinity than a comparable polypeptide comprising the wild-type Fc region binds Fc $\gamma$ RIIIA, and said polypeptide further specifically binds Fc $\gamma$ RIIB with a lower affinity than a comparable polypeptide comprising the wild-type Fc region binds Fc $\gamma$ RIIB, provided that said variant Fc region does not have an alanine at any of positions 256, 298, 333, or 334.

5. The polypeptide of claim 1 or 2, wherein said modification comprises at least one amino acid substitution in the Fc region.

6. The polypeptide of claim 1 or 2, wherein said amino acid modification comprises at least one amino acid modification in the CH2 domain of the Fc region.

7. The polypeptide of claim 6, wherein said amino acid modification comprises substitution of Pro 247 with another amino acid at that position.

8. The polypeptide of claim 1 or 2, wherein said amino acid modification comprises at least one amino acid modification in the CH3 domain of the Fc region.

9. The polypeptide of claim 8, wherein said amino acid modification comprises substitution at position 396 with another amino acid at that position.
10. The polypeptide of claim 1 or 2, wherein said amino acid modification comprises at least one amino acid modification in the CH2 domain and at least one amino acid  
5 modification in the CH3 domain of the Fc region.
11. The polypeptide of claim 6, wherein said amino acid modification in the CH2 domain comprises substitution at position 251, 292, 268, 288, 291, or 247 with another amino acid at that position.
12. The polypeptide of claim 8, wherein said amino acid modification in the CH3  
10 domain comprises substitution at position 347, 415, 399, 383, 384, 407, 395, or 396 with another amino acid at that position.
13. The polypeptide of claim 10, further comprising at least one amino acid modification in the hinge region of the Fc region.
14. The polypeptide of claim 1 or 2, wherein said amino acid modification comprises at  
15 least one amino acid modification in the hinge region of the Fc region.
15. The polypeptide of any of claims 1, 2, or 4 wherein the Fc region of the parent polypeptide is a human IgG Fc region.
16. The polypeptide of claim 15, wherein the human IgG Fc region is a human IgG1, IgG2, IgG3, or IgG4 Fc region.
- 20 17. The polypeptide of claim 1 or 2 wherein said polypeptide is an antibody.
18. An antibody comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said antibody specifically binds Fc $\gamma$ RIIIA with a greater affinity than a comparable antibody comprising the wild-type Fc region binds Fc $\gamma$ RIIIA, and said antibody further specifically  
25 binds Fc $\gamma$ RIIB with a lower affinity than a comparable antibody comprising the wild-type Fc region binds Fc $\gamma$ RIIB, provided that said variant Fc region does not have an alanine at any of positions 256, 298, 333, or 334.
19. The antibody of claim 17, wherein said antibody is a monoclonal antibody, a humanized antibody, or a human antibody.

20. A nucleic acid comprising a nucleotide sequence encoding the polypeptide of any of claims 1 or 2.
21. A vector comprising the nucleic acid of claim 20.
22. The vector of claim 21 which is an expression vector.
- 5 23. A host cell comprising the nucleic acid of claim 22.
24. A method for recombinantly producing the polypeptide of claims 1 or 2, said method comprising: (i) culturing in a medium a host cell comprising a nucleic acid encoding said polypeptide, under conditions suitable for the expression of said polypeptide; and (ii) recovery of said polypeptide from said medium.
- 10 25. The antibody of claims 17 or 18, wherein said antibody specifically binds Fc $\gamma$ RIIIA with at least two times greater affinity than a comparable antibody comprising the wild-type Fc region binds Fc $\gamma$ RIIIA.
26. A therapeutic antibody that specifically binds a cancer antigen, said therapeutic antibody comprising a variant Fc region, wherein said variant Fc region comprises at least
- 15 one amino acid modification relative to a wild-type Fc region, such that said therapeutic antibody specifically binds Fc $\gamma$ RIIIA with a greater affinity than the therapeutic antibody comprising the wild-type Fc region binds Fc $\gamma$ RIIIA, provided that said at least one amino acid modification is not solely a substitution at positions 329, 331, or 332, or does not have an alanine at any of positions 256, 290, 298, 312, 333, 334, 359, 360, or 430; a lysine at
- 20 position 330; a threonine at position 339; a methionine at position 320; a serine at position 326; an asparagine at position 326; an aspartic acid at position 326; a glutamic acid at position 326; a glutamine at position 334; a glutamic acid at position 334; a methionine at position 334; a histidine at position 334; a valine at position 334; or a leucine at position 334.
- 25 27. A therapeutic antibody that specifically binds a cancer antigen, said therapeutic antibody comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said therapeutic antibody specifically binds Fc $\gamma$ RIIIA with a greater affinity than a therapeutic antibody comprising the wild-type Fc region binds Fc $\gamma$ RIIIA, and said therapeutic antibody further
- 30 specifically binds Fc $\gamma$ RIIB with a lower affinity than a therapeutic antibody comprising the

wild-type Fc region binds FcγRIIB, provided that said variant Fc region does not solely have an alanine at any of positions 256, 298, 333, or 334.

28. The therapeutic antibody of claim 26 or 27, wherein said therapeutic antibody mediates antibody dependent cell mediated cytotoxicity 2-fold more effectively, than the  
5 therapeutic antibody comprising a wild-type Fc region.

29. The therapeutic antibody of claim 26 or 27, wherein said therapeutic antibody is Herceptin®, Rituxan®, IC14, PANOREX™, IMC-225, VITAXIN™, Campath 1H/LDP-03, LYMPHOCIDE™, or ZEVLIN™.

30. The therapeutic antibody of claim 26 or 27, wherein said cancer antigen is MAGE-1,  
10 MAGE-3, BAGE, GAGE-1, GAGE-2, N-acetylglucosaminyltransferase, p15, beta-catenin, MUM-1, CDK4, HER-2/neu, human papillomavirus-E6, human papillomavirus-E7, or MUC-1.

31. A method of treating cancer in a patient having a cancer characterized by a cancer antigen, said method comprising administering to said patient a therapeutically effective  
15 amount of a therapeutic antibody of claim 26 or 27.

32. The method of claim 31, wherein said cancer antigen is MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, N-acetylglucosaminyltransferase, p15, beta-catenin, MUM-1, CDK4, HER-2/neu, human papillomavirus-E6, human papillomavirus-E7, or MUC-1.

33. The method of claim 31, wherein said cancer antigen is a breast, ovarian, prostate,  
20 cervical, or pancreatic carcinoma antigen.

34. The method of claim 31 further comprising the administration of one or more additional cancer therapies.

35. The method of claim 34, wherein said additional cancer therapy is selected from the group consisting of chemotherapy, immunotherapy, radiation therapy, hormonal therapy, or  
25 surgery.

36. The method of claim 31, wherein said patient is human.

37. A pharmaceutical composition comprising a therapeutically effective amount of one or more of the polypeptides of claims 1 or 2, and a pharmaceutically acceptable carrier.

38. A pharmaceutical composition comprising a therapeutically effective amount of one or more of the antibodies of claims 17 or 18, and a pharmaceutically acceptable carrier.
39. A pharmaceutical composition comprising a therapeutically effective amount of one or more of the therapeutic antibodies of claims 26 or 27, and a pharmaceutically acceptable carrier.
40. The pharmaceutical composition of claims 26 or 27, further comprising one or more additional anti-cancer agents.
41. The pharmaceutical compositions of claim 40, wherein said anti-cancer agents is a chemotherapeutic agent, a radiation therapeutic agent, a hormonal therapeutic agent, or an immunotherapeutic agent.
42. A nucleic acid comprising a nucleotide sequence encoding a heavy chain of an antibody of any of claims 17 or 18.
43. A vector comprising the nucleic acid of claim 42.
44. The vector of claim 43 which is an expression vector.
45. A host cell comprising the nucleic acid of claim 44.
46. A method for recombinantly producing the antibody of claim 17 or 18, said method comprising: (i) culturing in a medium a host cell comprising a nucleic acid encoding said antibody, under conditions suitable for the expression of said antibody; and (ii) recovery of said antibody from said medium.
47. A method for producing a tetrameric Fc $\gamma$ R complex, wherein said tetrameric complex has an enhanced affinity for an Fc region, relative to the affinity of a monomeric Fc $\gamma$ R for the Fc region, comprising:
- (a) producing a fusion protein, such that a 15 amino acid AVITAG sequence is operably linked to the soluble region of Fc $\gamma$ R;
  - (b) biotinylating the protein produced in step (a);
  - (c) mixing the biotinylated protein produced in step (b) with streptaividn-phycoerythin in an appropriate molar ratio,

such that a tetrameric FcγR complex is formed.

48. The tetrameric FcγR complex produced by the method of claim 47.

49. The tetrameric FcγR complex of claim 48, wherein said complex binds an Fc region with an 8-fold higher affinity than a monomeric FcγR complex binds the Fc region.

5 50. The tetrameric FcγR complex of claim 48, wherein said complex binds an Fc region with a 10-fold higher affinity than a monomeric FcγR complex binds the Fc region.

51. The method of claim 47, wherein said tetrameric FcγR complex is a tetrameric FcγRIIIA complex, and said soluble region used in step (a) is the soluble region of FcγRIIIA.

10 52. The method of claim 47, wherein said tetrameric FcγR complex is a tetrameric FcγRIIB complex, and said soluble region used in step (a) is the soluble region of FcγRIIB.

53. The method of claim 47, wherein the protein produced in step (a) is biotinylated enzymatically.

15 54. The method of claim 47, wherein the protein produced in step (a) is biotinylated with *E. coli* Bir A enzyme.

55. The method of claim 47 wherein the biotinylated protein produced in step (a) is mixed with streptavidin-phycoerythrin in a 1:5 molar ratio (1X streptavidin-phycoerythrin : 5X biotinylated protein).

20 56. A method of treating or managing cancer in a patient having a cancer characterized by a cancer antigen, said method comprising administering to said patient a therapeutically effective amount of one or more of the antibodies of claims 17, 18, 26 or 27.

25 57. A method of treating cancer in a patient having a cancer characterized by a cancer antigen, said method comprising administering to said patient a therapeutically effective amount of one or more of the antibodies of claim 17, 18, 26 or 27 that specifically bind said cancer antigen.

58. A method of treating an autoimmune disorder in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of a molecule comprising a variant Fc region, wherein said variant Fc region comprises at least



one amino acid modification relative to a wild type Fc region, such that said molecule specifically binds Fc $\gamma$ RIIB with a greater affinity than a comparable molecule comprising the wild type Fc region, and said molecule further specifically binds Fc $\gamma$ RIIA with a lower affinity than a comparable molecule comprising the wild type Fc region.

5 59. The method of claim 58, wherein said autoimmune disorder is rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Rieter's Syndrome, psoriasis, or lupus erythematosus.

60. The method of claim 58 further comprising administering to said patient a therapeutically effective amount one or more anti-inflammatory agents.

10 61. The method of claim 58 further comprising administering to said patient a therapeutically effective amount one or more immunomodulatory agents.

62. The method of claim 61, wherein at least one immunomodulatory agent is a small organic molecule.

15 63. The method of claim 62, wherein the small organic molecule is methotrexate, leflunomide, cyclophosphamide, cyclosporin A, FK506, mycophenolate mofetil, rapamycin, mizoribine, deoxyspergualin, brequinar, malonitrolamide, steroid, or corticosteroid.

64. The method of claim 60, wherein at least one anti-inflammatory agents is a non-steroidal anti-inflammatory drug.

20 65. The method of claim 64, wherein the non-steroidal anti-inflammatory drug is aspirin, ibuprofen, diclofenac, nabumetone, naproxen, or ketoprofen.

66. A method of treating an infectious disease in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of a molecule comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild type Fc region, such that said molecule specifically  
25 binds Fc $\gamma$ RIIB with a greater affinity than a comparable molecule comprising the wild type Fc region, and said molecule further specifically binds Fc $\gamma$ RIIA with a lower affinity than a comparable molecule comprising the wild type Fc region.

67. The polypeptide of claims 1 or 2, wherein said polypeptide specifically binds Fc $\gamma$ RIIIA with a 4-fold greater affinity than a comparable polypeptide comprising the wild type Fc region binds Fc $\gamma$ RIIIA.
68. The polypeptide of claims 1 or 2, wherein said polypeptide specifically binds Fc $\gamma$ RIIIA with an 8-fold greater affinity than a comparable polypeptide comprising the wild type Fc region binds Fc $\gamma$ RIIIA
69. The polypeptide of claims 1 or 2, wherein said polypeptide specifically binds Fc $\gamma$ RIIIA with a 10-fold greater affinity than a comparable polypeptide comprising the wild type Fc region binds Fc $\gamma$ RIIIA
70. The polypeptide of claims 1 or 2, wherein said polypeptide specifically binds Fc $\gamma$ RIIIA with a 100-fold greater affinity than a comparable polypeptide comprising the wild type Fc region binds Fc $\gamma$ RIIIA
71. The antibody of claim 17 or 18, wherein said antibody specifically binds Fc $\gamma$ RIIIA with a 4-fold greater affinity than a comparable antibody comprising the wild type Fc region binds Fc $\gamma$ RIIIA.
72. The antibody of claim 17 or 18, wherein said antibody specifically binds Fc $\gamma$ RIIIA with an 8-fold greater affinity than a comparable antibody comprising the wild type Fc binds Fc $\gamma$ RIIIA.
73. The antibody of claim 17 or 18, wherein said antibody specifically binds Fc $\gamma$ RIIIA with a 10-fold greater affinity than a comparable antibody comprising the wild type Fc binds Fc $\gamma$ RIIIA.
74. The antibody of claim 17 or 18, wherein said antibody specifically binds Fc $\gamma$ RIIIA with a 100-fold greater affinity than a comparable antibody comprising the wild type Fc binds Fc $\gamma$ RIIIA.
75. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region, such that said polypeptide specifically binds Fc $\gamma$ RIIIA with a greater affinity than a comparable polypeptide comprising the wild-type Fc region, and said polypeptide further specifically binds Fc $\gamma$ RIIB with a lower affinity than a comparable polypeptide comprising the wild type Fc region binds Fc $\gamma$ RIIB, wherein said at least one amino acid modification comprises

a set of substitutions selected from the group consisting of a substitution at position 243 with isoleucine and at position 379 with leucine; a substitution at position 288 with asparagine, at position 330 with serine and at position 396 with leucine; a substitution at position 243 with leucine and at position 255 with leucine; a substitution at position 288 with methionine and at position 334 with glutamic acid; a substitution at position 316 with aspartic acid, at position 378 with valine, and at position 399 with glutamic acid; a substitution at position 315 with isoleucine, at position 379 with methionine, and at position 399 with glutamic acid; a substitution at position 243 with isoleucine, at position 379 with leucine, and at position 420 with valine; a substitution at position 392 with threonine and at position 396 with leucine; a substitution at position 293 with valine, at position 295 with glutamic acid, and at position 327 with threonine; a substitution at position 268 with asparagine and at position 396 with leucine; a substitution at position 319 with phenylalanine, at position 352 with leucine, and at position 396 with leucine; a substitution at position 248 with methionine; a substitution at position 247 with leucine and at position 420 with valine; a substitution 334 with glutamic acid and at position 292 with leucine.

76. The polypeptide of claim 75 wherein said polypeptide is an antibody.

77. The antibody of claim 76, wherein said antibody has an enhanced ADCC activity relative to a comparable antibody comprising the wild type fc region.

78. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 255 with leucine and at position 396 with leucine.

79. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 370 with glutamic acid and at position 396 with leucine.

80. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 392 with threonine and at position 396 with leucine.

81. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 221 with glutamic acid, at position 270 with glutamic acid, at position 308 with alanine, at position 311 with histidine, at position 396  
5 with leucine, and at position 402 with aspartic acid.

82. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 243 with leucine, at position 305 with isoleucine, at position 378 with aspartic acid, at position 404 with serine, and at position  
10 396 with leucine.

83. A polypeptide comprising a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification, wherein said at least one amino acid modification comprises substitution at position 284 with methionine, at position 298 with asparagine, at position 334 with glutamic acid, at position 355 with tryptophan, and at  
15 position 416 with threonine.